HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VICTOZA® safely and effectively. See full prescribing information for VICTOZA®.

VICTOZA® (liraglutide) injection, for subcutaneous use

Indications and Usage, Pediatric (1) 6/2019
Dosage and Administration, Pediatric (2.3) 6/2019
Warnings and Precautions (5.4) 6/2019

INDICATIONS AND USAGE
VICTOZA® is a glucagon-like peptide−1 (GLP−1) receptor agonist indicated:
• as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus (1).
• to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

DOSE AND ADMINISTRATION
• Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles (2.1).
• Inject VICTOZA® subcutaneously once-daily at any time of day, independently of meals, in the abdomen, thigh or upper arm (2.1).
• When using VICTOZA® with insulin, administer as separate injections. Never mix. (2.1).
• Adult Dosage: Initiate at 0.6 mg daily for one week then increase to 1.2 mg daily. If additional glycemic control is required, increase the dose to 1.8 mg daily after one week of treatment with the 1.2 mg daily dose (2.2).
• Pediatric Dosage: Initiate at 0.6 mg daily for at least one week. If additional glycemic control is required, increase the dose to 1.2 mg daily and if additional glycemic control is still required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose (2.3).

ADVERSE REACTIONS
• GI: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation (6.1).
• Hypoglycemia: Discontinue VICTOZA® and promptly seek medical advice (5.6).

DRUG INTERACTIONS
Oral Medications: VICTOZA® delays gastric emptying and may impact absorption of concomitantly administered oral medications (7).
Concomitant Use with an insulin secretagogue (e.g., Sulfonylurea) or with Insulin: when initiating, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonyluresa) or insulin to reduce the risk of hypoglycemia (7).

USE IN SPECIFIC POPULATIONS
• Pregnancy: VICTOZA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 6/2019
WARNING: RISK OF THYROID C-CELL TUMORS

- Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined [see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)].

- VICTOZA® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of VICTOZA® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA® [see Contraindications (4) and Warnings and Precautions (5.1)].

INDICATIONS AND USAGE

VICTOZA® is indicated:

- as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus,
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease [see Clinical Studies (14.3)].

Limitations of Use:

- VICTOZA® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.
- The concurrent use of VICTOZA® and prandial insulin has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing and Administration Instructions

- Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.
- Inject VICTOZA® subcutaneously once-daily at any time of day, independently of meals.
- Inject VICTOZA® subcutaneously in the abdomen, thigh or upper arm. No dose adjustment is needed if changing the injection site and/or timing.
- When using VICTOZA® with insulin, administer as separate injections. Never mix.
- It is acceptable to inject VICTOZA® and insulin in the same body region but the injections should not be adjacent to each other.
- If a dose is missed, resume the once-daily regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase the dose to make up for the missed dose.
- If more than 3 days have elapsed since the last VICTOZA® dose, reinject VICTOZA® at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinstitution of treatment. Upon reinstitution, VICTOZA® should be titrated at the discretion of the prescriber.

2.2 Adult Dosage

- Initiate VICTOZA® with a dose of 0.6 mg daily for one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control in adults. After one week at 0.6 mg per day, increase the dose to 1.2 mg daily.
- If additional glycemic control is required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose.

2.3 Pediatric Dosage

- Initiate VICTOZA® with a dose of 0.6 mg daily.
- After at least one week at 0.6 mg daily, the dose may be increased to 1.2 mg daily if additional glycemic control is required.
- If additional glycemic control is required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose.

3 DOSAGE FORMS AND STRENGTHS

Injection: 18 mg/mL (6 mg/mL) clear, colorless solution in a pre-filled, multi-dose pen that delivers 3 mL (1 mL, 1.8 mg, 3 mL, 6 mg/mL).

4 CONTRAINDICATIONS

- Medullary Thyroid Carcinoma

VICTOZA® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

- Hypersensitivity

VICTOZA® is contraindicated in patients with a prior serious hypersensitivity reaction to VICTOZA® or to any of the product components. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with VICTOZA® [see Warnings and Precautions (5.6)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice [see Nonclinical Toxicology (13.1)]. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether VICTOZA® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with VICTOZA® have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and VICTOZA® use in humans.

VICTOZA® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of VICTOZA® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA®. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Pancreatitis

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with VICTOZA®. After initiation of VICTOZA®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, VICTOZA® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, VICTOZA® should not be restarted.

In glycemic control trials of VICTOZA®, there have been 13 cases of pancreatitis among VICTOZA®-treated patients and 1 case in a comparator (gliamepride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with VICTOZA® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a VICTOZA®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholecystitis or alcohol abuse.

VICTOZA® has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on VICTOZA®.

5.3 Never Share a VICTOZA® Pen Between Patients

VICTOZA® pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

5.4 Use with Medications Known to Cause Hypoglycemia

Patients receiving VICTOZA® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin [see Adverse Reactions (6.1), Drug Interactions (7.2)].

In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with VICTOZA® regardless of concomitant antidiabetic therapies.

5.5 Renal Impairment

VICTOZA® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in VICTOZA®-treated patients [see Adverse Reactions (6.2)]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration [see Adverse Reactions (6.1)]. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including VICTOZA®. Use caution when initiating or escalating doses of VICTOZA® in patients with renal impairment [see Contraindications (4.8), Use in Specific Populations (8.6)].

5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with VICTOZA®. If a hypersensitivity reaction occurs, discontinue VICTOZA®, treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to VICTOZA® [see Contraindications (4.9)].

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with VICTOZA®.

5.7 Acute Gallbladder Disease

In the LEADER trial [see Clinical Studies (14.3)], 3.1% of VICTOZA®-treated patients versus 1.9% of placebo-treated patients reported an acute event of gallbladder disease, such as cholecystitis or cholecyctectomy. The majority of events required hospitalization or cholecystectomy. If cholecystitis is suspected, cholecystectomy needs to be performed.

5.8 Common Cold

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-Cell Tumors [see Warnings and Precautions (5.1)]
- Pancreatitis [see Warnings and Precautions (5.2)]
- Use with Medications Known to Cause Hypoglycemia [see Warnings and Precautions (5.4)]
- Renal Impairment [see Warnings and Precautions (5.5)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions

The safety of VICTOZA® in subjects with type 2 diabetes was evaluated in 5 glycemic control, placebo-controlled trials in adults and one trial of 52 weeks duration in pediatric patients 10 years of age and older [see Clinical Studies (14.1)]. The data in Table 1 reflect exposure of 1673 adult patients
to VICTOZA® and a mean duration of exposure to VICTOZA® of 37.3 weeks. The mean age of adult patients was 58 years, 4% were 75 years or older and 54% were male. The population was 79% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9.1 years and a mean HbA1c of 9.4%. Baseline estimated renal function was normal or mildly impaired in 88.1% and moderately impaired in 11.9% of the pooled population.

Table 1 shows common adverse reactions in adults, excluding hypoglycemia, associated with the use of VICTOZA®. These adverse reactions occurred more commonly on VICTOZA® than on placebo and occurred in at least 5% of patients treated with VICTOZA®. Overall, the type, and severity of adverse reactions in adolescents and children aged 10 years and above were comparable to that observed in the adult population.

Table 1 Adverse reactions reported in ≥5% of VICTOZA®-treated patients

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo N = 661</th>
<th>Liraglutide 1.2 mg N = 645</th>
<th>Liraglutide 1.8 mg N = 1024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Cumulative proportions were calculated combining studies using Cochran-Mantel-Haenszel weights.

In an analysis of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Other Adverse Reactions:

Gastrointestinal Adverse Reactions

In the pool of 5 glycemic control, placebo-controlled clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.5% of VICTOZA®-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

Injection site reactions

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of VICTOZA®-treated patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of VICTOZA®-treated patients discontinued due to injection site reactions.

Hypoglycemia

In 5 adult glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8% of VICTOZA®-treated patients (7.5 events per 1000 patient-years). Of these VICTOZA®-treated patients, 7 patients were concomitantly using a sulfonylurea.

Table 2 shows the incidence (%) and rate (episodes/patient year) of hypoglycemia in 26-Week Combination Therapy Placebo-controlled Trials.

Table 2 Adult Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in 26-Week Combination Therapy Placebo-controlled Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo Comparator</th>
<th>VICTOZA® Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-on to Metformin (N = 121)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient not able to self-treat</td>
<td>0</td>
<td>0.1 (0.001)</td>
</tr>
<tr>
<td>Patient able to self-treat</td>
<td>0.1 (0.005)</td>
<td>3.6 (0.35)</td>
</tr>
<tr>
<td>Add-on to Glimepiride (N = 114)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient not able to self-treat</td>
<td>0</td>
<td>0.1 (0.003)</td>
</tr>
<tr>
<td>Patient able to self-treat</td>
<td>2.6 (0.17)</td>
<td>7.5 (0.38)</td>
</tr>
<tr>
<td>Not classified</td>
<td>0</td>
<td>0.9 (0.05)</td>
</tr>
<tr>
<td>Add-on to Metformin + Rosiglitazone (N = 175)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient not able to self-treat</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient able to self-treat</td>
<td>4.6 (0.15)</td>
<td>7.9 (0.49)</td>
</tr>
<tr>
<td>Not classified</td>
<td>1.1 (0.03)</td>
<td>0.6 (0.01)</td>
</tr>
<tr>
<td>Add-on to Metformin + Glimepiride (N = 114)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient not able to self-treat</td>
<td>0</td>
<td>0.2 (0.06)</td>
</tr>
<tr>
<td>Patient able to self-treat</td>
<td>16.7 (0.95)</td>
<td>27.4 (0.16)</td>
</tr>
</tbody>
</table>

"Patient not able to self-treat" is defined as an event requiring the assistance of another person for treatment.

In a 26-week pediatric placebo-controlled clinical trial with a 26-week open-label extension, 21.2% of VICTOZA®-treated patients (mean age 14.6 years) with type 2 diabetes, had hypoglycemia with a blood glucose <54 mg/dL with or without symptoms (335 events per 1000 patient years). No severe hypoglycemic episodes occurred in the VICTOZA® treatment group (severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions).

Papillary thyroid carcinoma

In glycemic control trials of VICTOZA®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with VICTOZA® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

Cholelithiasis and cholecystitis

In glycemic control trials of VICTOZA®, the incidence of cholelithiasis was 0.3% in both VICTOZA®-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both VICTOZA®-treated and placebo-treated patients.

In the LEADER trial [see Clinical Studies (14.3)], the incidence of cholelithiasis was 1.5% (2.9 cases per 1000 patient years of observation) in VICTOZA®-treated patients. 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

Calcinonin

Calcinonin, a biological marker of MTC, was measured throughout the clinical development program. At the end of the glycemic control trials, adjusted mean serum calcitonin concentrations were higher in VICTOZA®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin concentrations were approximately 0.1 ng/L or less. Among patients with pretreatment calcitonin >20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of VICTOZA®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown.

VICTOZA® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with VICTOZA® compared to placebo.

6.2 Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with VICTOZA® may develop anti-liraglutide antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to liraglutide cannot be directly compared with the incidence of antibodies of other products.

Approximately 50-70% of VICTOZA®-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these VICTOZA®-treated patients. Cross-reacting anti-liraglutide antibodies to native GLP-1 (GLP-1) occurred in 6.9% of the VICTOZA®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the VICTOZA®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 2.3% of the VICTOZA®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the VICTOZA®-treated patients in the double-blind 26-week add-on combination therapy trials.

Antibody formation was not associated with reduced efficacy of VICTOZA® when comparing mean HbA1c of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA1c with VICTOZA® treatment.

In five double-blind glycemic control trials of VICTOZA®, events from a composite of adverse events potentially related to immunogenicity (e.g., urticaria, angioedema) occurred among 0.8% of VICTOZA®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for VICTOZA®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

In the LEADER trial [see Clinical Studies (14.3)], anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) VICTOZA®-treated patients with antibody measurements.

Of the 11 VICTOZA®-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed antibodies against native GLP-1.

In a clinical trial with pediatric patients 10 to 17 years [see Clinical Studies (14.2)], anti-liraglutide antibodies were detected in 1 (1.5%) VICTOZA®-treated patient at week 26 and 5 (8.5%) VICTOZA®-treated patients at week 52.
treated patients at week 53. None of the 5 had antibodies cross reactive to native GLP-1 or had neutralizing antibodies.

6.3 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of VICTOZA®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Medullary thyroid carcinoma
- Dehydration resulting from nausea, vomiting and diarrhea.
- Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis.
- Angioedema and anaphylactic reactions.
- Allergic reactions: rash and pruritus.
- Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

7 DRUG INTERACTIONS

7.1 Oral Medications

VICTOZA® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, VICTOZA® did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with VICTOZA®.

7.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating VICTOZA®, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia [see Warnings and Precautions (5.4) and Adverse Reactions (6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to VICTOZA® during pregnancy. VICTOZA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD [see Animal Data].

The estimated background risk of major birth defects for women with uncontrolled pre-gestational diabetes (Hemoglobin A1c >7) is 6 to 10%. The major birth defect rate has been reported to be as high as 20 to 25% in women with a Hemoglobin A1c >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Animal Data

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-3, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidney and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misslephron ureaphyryn and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scalpula), > 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilical) > 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bilurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F2 generation rats descended from liraglutide-treated rats compared to F2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.2 Lactation

Risk Summary

There are no data on the presence of VICTOZA® in human milk, the effects on the breastfed infant, or the effects on milk production. Liraglutide was present in milk of lactating rats [see Data]. Developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for VICTOZA® and any potential adverse effects on the breastfed infant from VICTOZA® or from the underlying maternal condition.

Data

In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

The safety and effectiveness of VICTOZA® as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients 10 years of age and older. Use of VICTOZA® for this indication is supported by a 26-week placebo-controlled clinical trial and a 26-week open-label extension in 134 pediatric patients 10 to 17 years of age with type 2 diabetes, a pediatric pharmacokinetic study, and studies in adults with type 2 diabetes mellitus [see Clinical Pharmacology (12.3) and Clinical Studies (14.1, 14.2)]. The risk of hypoglycemia was higher with VICTOZA® in pediatric patients regardless of concomitant antidiabetic therapies. The safety and effectiveness of VICTOZA® have not been established in pediatric patients less than 10 years of age.

8.5 Geriatric Use

In the VICTOZA® treatment arm of the glycemic control trials, a total of 832 (19.3%) of the patients were 65 to 74 years of age and 145 (3.4%) were 75 years of age and over. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In the VICTOZA® treatment arm of the LEADER trial [see Clinical Studies (14.3)], a total of 1738 (37.2%) patients were 65 to 74 years of age, 401 (8.6%) were 75 to 84 years of age, and 17 (0.4%) were 85 years of age or older at baseline. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

No dose adjustment of VICTOZA® is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)]. The safety and efficacy of VICTOZA® was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m²) [see Clinical Studies (14.1)].

In the VICTOZA® treatment arm of the LEADER trial [see Clinical Studies (14.3)], 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function.

There is limited experience with VICTOZA® in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis [see Warnings and Precautions (5.5) and Adverse Reactions (6.2)]. Use caution in patients who experience dehydration.

8.7 Hepatic Impairment

There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, VICTOZA® should be used with caution in this patient population. No dose adjustment of VICTOZA® is recommended for patients with hepatic impairment [see Clinical Pharmacology (12.3)].

8.8 Gastroesophageal Reflux Disease

VICTOZA® slows gastric emptying. VICTOZA® has not been studied in patients with pre-existing gastroesophageal reflux disease.

10 OVERDOSAGE

Overdoses have been reported in clinical trials and post-marketing use of VICTOZA®. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

VICTOZA® contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is C172H334Na2O70 and the molecular weight is 3751.2 Daltons.

The structural formula (Figure 1) is:

![Figure 1 Structural Formula of Liraglutide](image-url)

VICTOZA® is a clear, colorless or almost colorless solution. Each 1 mL of VICTOZA® solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg;
propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Each pre-filled pen contains a 3 mL solution of VICTOZA® equivalent to 18 mg liraglutide (free-base, anhydrous).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

Liraglutide is stable to a wide range of pH and is degraded by aminopeptidases at pH 11.5. Liraglutide is metabolized by metabolism by DPP-IV and NEP.

12.2 Pharmacodynamics

VICTOZA’s pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as VICTOZA in fasted, premeal and postprandial glucose based on results provided adequate (8-12 h) would coincide with the absorption peak of the co-administered drugs. and insulin detemir when separate AVmax of liraglutide over 24 hours was approximately 128 ng/mL. AUC∞ of single subcutaneous administration as VICTOZA was delayed up to 15 minutes. Administration of the interacting drugs was timed so that Cmax of VICTOZA (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose VICTOZA® 7.5 mg/kg (~0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

Glucagon secretion VICTOZA® lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of VICTOZA® 7.5 mg/kg (~0.7 mg) did not impair glucagon response to low glucose concentrations.

Gastric emptying VICTOZA® causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Cardiac Electrophysiology (QTc)

The effect of VICTOZA® on cardiac repolarization was tested in a QTc study. VICTOZA® at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

12.3 Pharmacokinetics

Absorption – Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (Cmax) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, Cmax and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg VICTOZA®, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. AUC∞ was equivalent between upper arm and abdomen, and between upper arm and thigh. AUC∞ from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution – The mean apparent volume of distribution after subcutaneous administration of VICTOZA® 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of VICTOZA® is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>80%).

Metabolism – During the initial 24 hours following administration of a single [H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Elimination – Following a [H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making VICTOZA® suitable for once daily administration.

Specific Populations

Elderly - Age had no effect on the pharmacokinetics of VICTOZA® based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age (see Use in Specific Populations (8.5)).

Gender - Based on the results of population pharmacokinetic analyses, females have 25% lower plasma exposures over the body weight range of 40 – 180 kg evaluated in the clinical trials. Liraglutide was not studied in patients with body weight >160 kg.

Pediatric - A population pharmacokinetic analysis was conducted for VICTOZA® using data from 72 pediatric subjects (10 to 17 years of age) with type 2 diabetes. The pharmacokinetic profile of VICTOZA® in the pediatric subjects was consistent with that in adults.

Renal Impairment - The single-dose pharmacokinetics of VICTOZA® were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) and moderate (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 23% and 30% lower, respectively (see Use in Specific Populations (8.6)).

Hepatic Impairment - The single-dose pharmacokinetics of VICTOZA® were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively (see Use in Specific Populations (8.7)).

Drug Interactions

In vitro assessment of drug-drug interactions VICTOZA® has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interactions The drug-drug interaction studies were performed at steady state with VICTOZA® 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to reach the maximum dose of 1.8 mg/day. Administration of the interacting drugs was timed so that Cmax of VICTOZA® (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Digoxin A single dose of digoxin 1 mg was administered 7 hours after the dose of VICTOZA® at steady state. The co-administration with VICTOZA® resulted in a reduction of digoxin AUC by 16%, Cmax decreased by 31%. Digoxin median time to maximal concentration (Tmax) was delayed from 1 h to 1.5 h.

Lisinopril A single dose of lisinopril 20 mg was administered 5 minutes after the dose of VICTOZA® at steady state. The co-administration with VICTOZA® resulted in a reduction of lisinopril AUC by 15%, Cmax decreased by 27%. Lisinopril median T max was delayed from 6 h to 8 h with VICTOZA®.

Atorvastatin VICTOZA® did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of VICTOZA® at steady state. Atorvastatin Cmax was decreased by 38% and median Tmax was delayed from 1 h to 3 h with VICTOZA®.

Acetaminophen VICTOZA® did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of VICTOZA® at steady state. Acetaminophen Cmax was decreased by 31% and median Tmax was delayed up to 15 minutes.

Griselutitin VICTOZA® did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with VICTOZA® at steady state. Griseofulvin Cmax increased by 37% while median Tmax did not change.

Oral Contraceptives A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of VICTOZA® at steady state. VICTOZA® lowered ethinylestradiol and levonorgestrel Cmax by 12% and 13%, respectively. There was no effect of VICTOZA® on the overall exposure (AUC) of ethinylestradiol. VICTOZA® increased the levonorgestrel AUC∞ by 18%. VICTOZA® delayed Tmax for both ethinylestradiol and levonorgestrel by 1.5 h.

Insulin Detemir No pharmacokinetic interaction was observed between VICTOZA® and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Unit/kg (single-dose) and VICTOZA® 1.8 mg (steady state) were administered in patients with type 2 diabetes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was
seen in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males at 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in controls, 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in controls, 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats.

Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the RERaianged during Transfection (RET) proto-oncogene in thyroid C-cells.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies [see Boxed Warning and Warnings and Precautions (5.1)].

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose in vivo micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a dose yielding an estimated systemic exposure 11-times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

In glycemic control trials, VICTOZA® has been studied as monotherapy and in combination with one or two oral anti-diabetic medications or basal insulin. VICTOZA® was also studied in a cardiovascular outcomes trial (LEADER trial).

In each of the placebo controlled trials, treatment with VICTOZA® produced clinically and statistically significant improvements in hemoglobin A1c and fasting plasma glucose (FPG) compared to placebo. All VICTOZA®-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. VICTOZA® 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance [see Dosage and Administration (2)].

Monotherapy

In this 52-week trial, 746 patients were randomized to VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with VICTOZA® 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA1c compared to glimepiride (Table 3). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the VICTOZA® 1.8 mg treatment group, 6.0% in the VICTOZA® 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group.

The mean age of participants was 53 years, and the mean duration of diabetes was 5 years. Participants were 49.7% male, 77.5% White, 12.6% Black or African American and 35.0% of Hispanic ethnicity. The mean BMI was 33.1 kg/m².

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The mean age of participants was 53 years, and the mean duration of diabetes was 5 years. Participants were 49.7% male, 77.5% White, 12.6% Black or African American. The mean BMI was 33.1 kg/m².

### Table 3 Results of a 52-week monotherapy trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intent-to-Treat Population (N)</th>
<th>HbA1c (%) (Mean)</th>
<th>Change from baseline (adjusted mean)</th>
<th>95% Confidence Interval</th>
<th>Direction from glimepiride arm (adjusted mean)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VICTOZA® 1.8 mg</strong></td>
<td>246</td>
<td>6.5</td>
<td>-2.5</td>
<td>(-0.5, -1)</td>
<td><em>(p-value &lt; 0.05)</em></td>
<td><em>(p-value &lt; 0.0001)</em></td>
</tr>
<tr>
<td><strong>VICTOZA® 1.2 mg</strong></td>
<td>251</td>
<td>6.5</td>
<td>-1.1</td>
<td>(-0.8, -0.4)</td>
<td><em>(p-value = 0.0014 for VICTOZA® 1.2 mg compared to glimepiride)</em></td>
<td><em>(p-value &lt; 0.0001)</em></td>
</tr>
<tr>
<td><strong>Glimepiride 8 mg</strong></td>
<td>246</td>
<td>8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p-value < 0.05
** p-value < 0.0001

*Intent-to-treat population using last observation on study

### Figure 3 Mean HbA1c for patients who completed the 52-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 52 (Monotherapy)

### Combination Therapy

#### Add-on to Metformin

In this 26-week trial, 1091 patients were randomized to VICTOZA® 0.6 mg, VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, placebo, or glimepiride 4 mg (one-half of the maximal approved dose in the United States), all as add-on to metformin. Randomization occurred after a 6-week run-in period consisting of a 3-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day. Treatment with VICTOZA® 1.2 mg and 1.8 mg as add-on to metformin resulted in a significant mean HbA1c reduction relative to placebo add-on to metformin and resulting in a similar mean HbA1c reduction relative to glimepiride 4 mg add-on to metformin (Table 4). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the VICTOZA® 1.8 mg + metformin treatment group, 3.3% in the VICTOZA® 1.2 mg + metformin treatment group, and 3.7% in the glimepiride + metformin treated group.

The mean age of participants was 57 years, and the mean duration of diabetes was 7 years. Participants were 53.2% male, 67.1% White and 24.2% Black or African American. The mean BMI was 31.0 kg/m².
In this 26-week trial, 1041 patients were randomized to VICTOZA® 1.2 mg once-daily, VICTOZA® 1.8 mg once-daily or sitagliptin 100 mg once-daily, all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased to 4 mg/day. The doses of glimepiride could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

The mean age of participants was 57 years, and the mean duration of diabetes was 8 years. Participants were 55.7% male, 91.3% White, 5.6% Black or African American and 12.5% of Hispanic ethnicity. The mean BMI was 32.8 kg/m².

The primary endpoint was the change in HbA¹c from baseline to week 26, with a clinically meaningful change of at least 0.5% from baseline. The study also evaluated additional efficacy endpoints, such as the percentage of patients achieving HbA¹c <7%, changes in fasting plasma glucose, body weight, and other safety and tolerability outcomes. All patients entered a 2-week, 1:1 double-blind, placebo-controlled run-in period after 4 weeks of open-label treatment with VICTOZA® 1.2 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with VICTOZA® 1.8 mg and metformin and 12.2% in the group randomized to add-on therapy with insulin detemir.

The mean BMI of participants was 34.0 kg/m², and the mean duration of diabetes was 6 years. Participants were 55.7% male, 91.3% White, 5.6% Black or African American and 12.5% of Hispanic ethnicity. The mean BMI was 32.8 kg/m².

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The primary endpoint was the change in HbA¹c from baseline to week 26, with a clinically meaningful change of at least 0.5% from baseline. The study also evaluated additional efficacy endpoints, such as the percentage of patients achieving HbA¹c <7%, changes in fasting plasma glucose, body weight, and other safety and tolerability outcomes. All patients entered a 2-week, 1:1 double-blind, placebo-controlled run-in period after 4 weeks of open-label treatment with VICTOZA® 1.2 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with VICTOZA® 1.8 mg and metformin and 12.2% in the group randomized to add-on therapy with insulin detemir.

The mean BMI of participants was 34.0 kg/m², and the mean duration of diabetes was 6 years. Participants were 55.7% male, 91.3% White, 5.6% Black or African American and 12.5% of Hispanic ethnicity. The mean BMI was 32.8 kg/m².

The primary endpoint was the change in HbA¹c from baseline to week 26, with a clinically meaningful change of at least 0.5% from baseline. The study also evaluated additional efficacy endpoints, such as the percentage of patients achieving HbA¹c <7%, changes in fasting plasma glucose, body weight, and other safety and tolerability outcomes. All patients entered a 2-week, 1:1 double-blind, placebo-controlled run-in period after 4 weeks of open-label treatment with VICTOZA® 1.2 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with VICTOZA® 1.8 mg and metformin and 12.2% in the group randomized to add-on therapy with insulin detemir.
In this 26-week, open-label trial, 533 patients were randomized to VICTOZA® 1.2 mg, VICTOZA® 1.8 mg or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2000 mg). Patients underwent a 9 week run-in period (3-week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial. The mean age of participants was 55 years, and the mean duration of diabetes was 9 years. Participants were 61.6% male, 84.2% White, 10.2% Black or African American and 16.4% of Hispanic ethnicity. The mean BMI was 33.9 kg/m².

Treatment with VICTOZA® as add-on to metformin and thiazolidinediones produced a statistically significant reduction in mean HbA1c compared to placebo add-on to metformin and rosiglitazone (Table 10). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the VICTOZA® 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the VICTOZA® 1.2 mg + metformin + rosiglitazone treatment group, and 1.6% in the placebo + metformin + rosiglitazone treatment group.

### Table 8 Results of a 26-week trial of VICTOZA® as add-on to metformin and sulfonylurea

<table>
<thead>
<tr>
<th></th>
<th>VICTOZA® 1.8 mg + Metformin + Glimepiride</th>
<th>Placebo + Metformin + Glimepiride</th>
<th>Insulin glargine® + Metformin + Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat Population (N)</td>
<td>270</td>
<td>114</td>
<td>232</td>
</tr>
<tr>
<td>HbA1c (%) (Mean)</td>
<td>8.0</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.8</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.3</td>
<td>-0.4</td>
<td>-1.1</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-1.9, -0.5)</td>
<td>(-1.1, -0.7)</td>
<td>(-1.1, -0.9)</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA1c ≤7%</td>
<td>53</td>
<td>15</td>
<td>46</td>
</tr>
</tbody>
</table>

### Table 9 Results of a 26-week open-label trial of VICTOZA® as add-on to metformin and sulfonylurea

<table>
<thead>
<tr>
<th></th>
<th>VICTOZA® 1.8 mg + Metformin + Rosiglitazone</th>
<th>VICTOZA® 1.2 mg + Metformin + Rosiglitazone</th>
<th>Placebo + Metformin + Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat Population (N)</td>
<td>178</td>
<td>177</td>
<td>175</td>
</tr>
<tr>
<td>HbA1c (%) (Mean)</td>
<td>8.5</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.6</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-1.1, -0.8)</td>
<td>(-1.1, -0.8)</td>
<td>(-0.5, -0.2)</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA1c ≤7%</td>
<td>54</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

### Table 10 Results of a 26-week trial of VICTOZA® as add-on to metformin and thiazolidinediones

<table>
<thead>
<tr>
<th></th>
<th>VICTOZA® 1.8 mg + Metformin + Rosiglitazone</th>
<th>VICTOZA® 1.2 mg + Metformin + Rosiglitazone</th>
<th>Placebo + Metformin + Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat Population (N)</td>
<td>114</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>Body Weight (kg) (Mean)</td>
<td>83.5</td>
<td>83.5</td>
<td>83.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>83.5</td>
<td>83.5</td>
<td>83.5</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.3</td>
<td>-0.3</td>
<td>-0.3</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-0.5, -0.1)</td>
<td>(-0.5, -0.1)</td>
<td>(-0.5, -0.1)</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA1c ≤7%</td>
<td>54</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>
VICTOZA® (liraglutide) injection, for subcutaneous use

In this 26-week, double-blind, randomized, placebo-controlled, parallel-group trial, 279 patients with type 2 diabetes mellitus, as per MDRD formula (eGFR 30–59 mL/min/1.73 m²), were randomized to VICTOZA® or placebo once daily. VICTOZA® was added to the patient’s stable pre-trial antidiabetic regimen (insulin therapy and/or metformin, pioglitazone, or sulfonylurea). The dose of VICTOZA® was escalated according to approved labeling to achieve a dose of 1.8 mg per day. The insulin dose was reduced by 20% at randomization for patients with baseline HbA1c ≤ 8% and fixed until irinlglutide dose escalation was complete. Dose reduction of insulin and SU was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

The mean age of participants was 67 years, and the mean duration of diabetes was 15 years. Participants were 50.5% male, 92.3% White, 6.6% Black or African American, and 7.2% of Hispanic ethnicity. The mean BMI was 39.9 kg/m². Approximately half of patients had an eGFR between 30 and <45 mL/min/1.73 m². Treatment with VICTOZA® resulted in a statistically significant reduction in HbA1c from baseline at Week 26 compared to placebo (see Table 11). 123 patients reached the 1.8 mg dose of VICTOZA®.

Table 11 Results of a 26-week trial of VICTOZA® compared to placebo in Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Intent to Treat Population (N)</th>
<th>VICTOZA® 1.8 mg + insulin and/or OAD</th>
<th>Placebo + insulin and/or OAD</th>
<th>Treatment difference [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>8.1</td>
<td>8.0</td>
<td>-0.1 [-0.2, -0.0]</td>
</tr>
<tr>
<td>Change from baseline (estimated mean)±SE</td>
<td>-0.9</td>
<td>-0.4</td>
<td>-0.5 [-0.8, -0.3]</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>-0.8, -0.3</td>
<td>-0.4, -0.2</td>
<td>-0.5, -0.3</td>
</tr>
<tr>
<td>Proportion achieving HbA1c &lt; 7%</td>
<td>39.3</td>
<td>19.7</td>
<td>20.6 [17.6, 23.7]</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>171</td>
<td>167</td>
<td>-4 [-8, 0]</td>
</tr>
<tr>
<td>Change from baseline (estimated mean)±SE</td>
<td>-22</td>
<td>-10</td>
<td>-12 [-20, -4]</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>-23, -8</td>
<td>-19, -5</td>
<td>-14, -6</td>
</tr>
</tbody>
</table>

*Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit. Multiple imputation model modeled ‘wash out’ of the treatment effect for patients having missing data who discontinued treatment. Early treatment discontinuation, before week 26, occurred in 25% and 22% of VICTOZA® and placebo patients, respectively. Based on the known number of subjects achieving HbA1c < 7%. When applying the multiple imputation method described in b above, the estimated percent achieving HbA1c < 7% are 47.5% and 24.9% for VICTOZA® and placebo, respectively. Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit.

14.2 Glycemic Control Trial in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus

VICTOZA® was evaluated in a 26-week, double-blind, randomized, parallel group, placebo controlled multi-center trial (NCT01541215), in 134 pediatric patients with type 2 diabetes aged 10 years and older. Patients were randomized to VICTOZA® once-daily or placebo once-daily in combination with metformin with or without basal insulin treatment. All patients were on a metformin dose of 1000 to 2000 mg prior to randomization. The basal insulin dose was decreased by 20% at randomization and VICTOZA® was titrated weekly by 0.6 mg for 2 to 3 weeks based on tolerability and an average fasting glucose goal of ≤110 mg/dL. The mean age was 14.6 years: 29.9% were ages 10-14 years, and 70.1% were greater than 14 years of age. 38.1% were male, 64.9% were White, 13.4% were Asian, 11.9% were Black or African American; 29.1% were of Hispanic or Latino ethnicity. The mean BMI was 33.9 kg/m² and the mean BMI SDS was 2.9. 18.7% of patients were using basal insulin at baseline. The mean duration of diabetes was 1.9 years and the mean HbA1c was 7.8%.

At week 26, treatment with VICTOZA® was superior in reducing HbA1c from baseline versus placebo. The estimated treatment difference in HbA1c reduction from baseline between VICTOZA® and placebo was -1.06% with a 95% confidence interval of [-1.65%, -0.46%] (see Table 12).

Table 12 Results at week 26 in a trial comparing VICTOZA® in combination with metformin with or without basal insulin versus Placebo in combination with metformin with or without basal insulin in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>VICTOZA®+metformin+</th>
<th>Placebo+metformin+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>basal insulin</td>
<td>basal insulin</td>
</tr>
<tr>
<td>N</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.9</td>
<td>7.7</td>
</tr>
<tr>
<td>End of 26 weeks</td>
<td>7.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Adjusted mean change from baseline after 26 weeks</td>
<td>-0.04</td>
<td>0.42</td>
</tr>
<tr>
<td>Treatment difference [95%CI]</td>
<td>VICTOZA® vs Placebo</td>
<td>-1.06 [-1.65, -0.46]</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA1c&lt;7%</td>
<td>63.7</td>
<td>36.5</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>Baseline</td>
<td>End of 26 weeks</td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>147</td>
</tr>
<tr>
<td>Adjusted mean change from baseline after 26 weeks</td>
<td>-19.4</td>
<td>14.4</td>
</tr>
<tr>
<td>Treatment difference [95%CI]</td>
<td>VICTOZA® vs Placebo</td>
<td>-33.83 [-55.74, -11.92]</td>
</tr>
</tbody>
</table>

*p-value <0.001
**p-value <0.05

14.3 Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The LEADER trial (NCT01173048) was a multi-national, multi-center, placebo-controlled, double-blind trial. In this study, 9340 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to VICTOZA® 1.8 mg or placebo for a median duration of 3.5 years. The study compared the risk of major adverse cardiovascular events between VICTOZA® and placebo when these were added to, and used concomitantly with, background standard of care treatments for type 2 diabetes: metformin, sulfonylurea and/or basal insulin. Use of DPP-4 inhibitors and other GLP-1 receptor agonists was excluded by protocol and SGLT-2 inhibitors were either not approved or not widely available. At baseline, cardiovascular disease risk factors and baseline as a covariate, all nested within visit. Significance was determined using an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate.

The LEADER trial (NCT01179048) was a multi-national, multi-center, placebo-controlled, double-blind trial. In this study, 9340 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to VICTOZA® 1.8 mg or placebo for a median duration of 3.5 years. The study compared the risk of major adverse cardiovascular events between VICTOZA® and placebo when these were added to, and used concomitantly with, background standard of care treatments for type 2 diabetes: metformin, sulfonylurea and/or basal insulin. Use of DPP-4 inhibitors and other GLP-1 receptor agonists was excluded by protocol and SGLT-2 inhibitors were either not approved or not widely available. At baseline, cardiovascular disease risk factors and baseline as a covariate, all nested within visit. Significance was determined using an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate.

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority against Placebo Both With or Without metformin and/or Sulfonylurea and/or Basal or Premix insulin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment

In this 26-week, double-blind, randomized, placebo-controlled, parallel-group trial, 279 patients with type 2 diabetes mellitus, as per MDRD formula (eGFR 30–59 mL/min/1.73 m²), were randomized to VICTOZA® or placebo once daily. VICTOZA® was added to the patient’s stable pre-trial antidiabetic regimen (insulin therapy and/or metformin, pioglitazone, or sulfonylurea). The dose of VICTOZA® was escalated according to approved labeling to achieve a dose of 1.8 mg per day. The insulin dose was reduced by 20% at randomization for patients with baseline HbA1c ≤ 8% and fixed until irinlglutide dose escalation was complete. Dose reduction of insulin and SU was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

The mean age of participants was 67 years, and the mean duration of diabetes was 15 years. Participants were 50.5% male, 92.3% White, 6.6% Black or African American, and 7.2% of Hispanic ethnicity. The mean BMI was 39.9 kg/m². Approximately half of patients had an eGFR between 30 and <45 mL/min/1.73 m². Treatment with VICTOZA® resulted in a statistically significant reduction in HbA1c from baseline at Week 26 compared to placebo (see Table 11). 123 patients reached the 1.8 mg dose of VICTOZA®.
VICTOZA® (liraglutide) injection, for subcutaneous use

Acute Gallbladder Disease
Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up.

Never Share a VICTOZA® Pen Between Patients
Advise patients that they must never share a VICTOZA® pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.

Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of VICTOZA®. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking VICTOZA® and seek medical advice promptly if such symptoms occur [see Warnings and Precautions (5.6)].

Jaundice and Hepatitis
Inform patients that jaundice and hepatitis have been reported during postmarketing use of liraglutide. Instruct patients to contact their physician if they develop jaundice.

Instructions
Advise patients that the most common side effects of VICTOZA® are headache, nausea and diarrhea. Nausea is most common when first starting VICTOZA®, but decreases over time in the majority of patients and does not typically require discontinuation of VICTOZA®.

Inform patients not to take an extra dose of VICTOZA® to make up for a missed dose. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. If more than 3 days have elapsed since the last dose, advise the patient to reinitiate VICTOZA® at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. VICTOZA® should be titrated at the discretion of the prescribing physician [see Dosage and Administration (2)].

Dehydration and Renal Failure
Advise patients treated with VICTOZA® of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis.

Pancreatitis
Inform patients of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue VICTOZA® promptly and contact their physician if persistent severe abdominal pain occurs [see Warnings and Precautions (5.2)].

Figure 5 Kaplan-Meier: Time to First Occurrence of a MACE in the LEADER Trial (Patients with T2DM and Atherosclerotic CVD)

Table 13 Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the LEADER Trial (Patients with T2DM and Atherosclerotic CVD)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>VICTOZA® N=4658</th>
<th>Placebo N=4672</th>
<th>Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (MACE) (time to first occurrence)</td>
<td>608 (13.0%)</td>
<td>694 (14.9%)</td>
<td>0.87 (0.78; 0.97)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarctiona</td>
<td>281 (6.0%)</td>
<td>317 (6.8%)</td>
<td>0.88 (0.75; 1.03)</td>
</tr>
<tr>
<td>Non-fatal strokea</td>
<td>159 (3.4%)</td>
<td>177 (3.8%)</td>
<td>0.89 (0.72; 1.11)</td>
</tr>
<tr>
<td>Cardiovascular deatha</td>
<td>219 (4.7%)</td>
<td>278 (6%)</td>
<td>0.78 (0.68; 0.93)</td>
</tr>
</tbody>
</table>

*aFull analysis set (all randomized patients)
*b Cox-proportional hazards model with treatment as a factor
*c p-value for superiority (2-sided) 0.011
*d Number and percentage of first events

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
VICTOZA® Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes:

2 x VICTOZA® pen NDC 0169-4060-12
3 x VICTOZA® pen NDC 0169-4060-13

Each VICTOZA® pen is for use by a single patient. A VICTOZA® pen must never be shared between patients, even if the needle is changed.

16.2 Recommended Storage
Prior to first use, VICTOZA® should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C) (Table 14). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA® and do not use VICTOZA® if it has been frozen.

After initial use of the VICTOZA® pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F, 15°C to 30°C) or in a refrigerator (36°F to 46°F, 2°C to 8°C). Keep the pen cap on when not in use. VICTOZA® should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA® pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.

Table 14 Recommended Storage Conditions for the VICTOZA® Pen

<table>
<thead>
<tr>
<th>Prior to first use</th>
<th>After first use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated 36°F to 46°F (2°C to 8°C)</td>
<td>Room Temperature 59°F to 86°F (15°C to 30°C)</td>
</tr>
<tr>
<td>Until expiration date</td>
<td>30 days</td>
</tr>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION

FDA-Approved Medication Guide

See separate leaflet.

Risk of Thyroid C-cell Tumors
Inform patients that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician [see Boxed Warning and Warnings and Precautions (5.1)].

Dehydration and Renal Failure
Advise patients treated with VICTOZA® of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis.

Pancreatitis
Inform patients of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue VICTOZA® promptly and contact their physician if persistent severe abdominal pain occurs [see Warnings and Precautions (5.2)].
Victoza® (liraglutide) injection, for subcutaneous use  Medication Guide

Read this Medication Guide before you start using VICTOZA® and each time you get a refill.

What is the most important information I should know about VICTOZA®?

VICTOZA® may cause serious side effects, including:
• Possible thyroid tumors, including cancer. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, VICTOZA® and medicines that work like VICTOZA® caused thyroid tumors, including thyroid cancer. It is not known if VICTOZA® will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
• Do not use VICTOZA® if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Who should not use VICTOZA®?

Do not use VICTOZA® if:
• you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
• you are allergic to liraglutide or any of the ingredients of VICTOZA®. See the end of this Medication Guide for a complete list of ingredients in VICTOZA®.

What is VICTOZA®?

VICTOZA® is an injectable prescription medicine used:
• along with diet and exercise to lower blood sugar (glucose) in adults and children who are 10 years of age and older with type 2 diabetes mellitus.
• to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes mellitus with known heart disease.
VICTOZA® is not for use in people with type 1 diabetes or people with diabetic ketoacidosis. It is not known if VICTOZA® can be used with mealtime insulin. It is not known if VICTOZA® is safe and effective to lower blood sugar (glucose) in children under 10 years of age.

Why should I use VICTOZA®?

• Your healthcare provider should show you how to use VICTOZA® before you use it for the first time.
• Use VICTOZA® 1 time each day, at any time of the day.
• Do not change (rotate) your injection site with each injection. Do not use the same site for each injection.
• You may give other people a serious infection, or get a serious infection from them.

Your dose of VICTOZA® and other diabetes medicines may need to change because of:
• change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What are the possible side effects of VICTOZA®?

VICTOZA® may cause serious side effects, including:
• See “What is the most important information I should know about VICTOZA®?”
• Inflammation of your pancreas (pancreatitis). Stop using VICTOZA® and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
• Low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use VICTOZA® with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. In children who are 10 years of age and older, the risk for low blood sugar may be higher with VICTOZA® regardless of use with another medicine that can also lower blood sugar.

Signs and symptoms of low blood sugar may include:
• Dizziness or light-headedness
• Anxiety, irritability, or mood changes
• Slurred speech
• Confusion or drowsiness
• Weakness
• Fast heartbeat
• Kidney problems (kidney failure). In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.
• Serious allergic reactions. Stop using VICTOZA® and get medical help right away, if you have any symptoms of a serious allergic reaction including:
  • Swelling of your face, lips, tongue or throat
  • Problems breathing or swallowing
  • Severe rash or itching
• Gallbladder problems. Gallbladder problems have happened in some people who take VICTOZA®.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of VICTOZA®.

How should I use VICTOZA®?

• Read the Instructions for Use that comes with VICTOZA®.
• Use VICTOZA® exactly as your healthcare provider tells you to.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of VICTOZA®.

Active Ingredient: Liraglutide

Inactive Ingredients: Disodium phosphate dihydrate, propylene glycol, phenol and water for injection.
Instructions for Use
Victoza® (liraglutide) injection

First read the Medication Guide that comes with your Victoza® pen and then read this Patient Instructions for Use for information about how to use your Victoza® pen the right way. These instructions do not take the place of talking with your healthcare provider about your medical condition or your treatment.

Do not share your Victoza® Pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Your Victoza® pen contains 3 mL of Victoza® and will deliver doses of 0.6 mg, 1.2 mg or 1.8 mg. The number of doses that you can take with a Victoza® pen depends on the dose of medicine that is prescribed for you. Your healthcare provider will tell you how much Victoza® to take.

Victoza® pen should be used with Novo Nordisk disposable needles. Talk to your healthcare provider or pharmacist for more information about needles for your Victoza® pen.

Important Information
- Always use a new needle for each injection to prevent contamination.
- Always remove the needle after each injection, and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage of liraglutide, blocked needles and inaccurate dosing.
- Keep your Victoza® pen and all medicines out of the reach of children.
- If you drop your Victoza® pen, repeat “First Time Use For Each New Pen” (steps A through D).
- Be careful not to bend or damage the needle.
- Do not use the cartridge scale to measure how much Victoza® to inject.
- Be careful when handling used needles to avoid needle stick injuries.
- You can use your Victoza® pen for up to 30 days after you use it the first time.

First Time Use for Each New Pen
Step A. Check the Pen
- Take your new Victoza® pen out of the refrigerator.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your Victoza® pen.
- Pull off pen cap (See Figure H).
- Check Victoza® in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.

Step B. Attach the Needle
- Remove protective tab from outer needle cap.
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure (See Figure I).
- Pull off outer needle cap.
- Do not throw away (See Figure J).
- Pull off inner needle cap and throw away (See Figure K). A small drop of liquid may appear. This is normal.

Step C. Dial to the Flow Check Symbol
This step is done only Once for each new pen and is Only required the first time you use a new pen.
- Turn dose selector until flow check symbol (**) lines up with pointer (See Figure E). The flow check symbol does not administer the dose as prescribed by your healthcare provider.
- To select the dose prescribed by your healthcare provider, continue to Step G under “Routine Use”.

Step D. Prepare the Pen
- Hold pen with needle pointing up.
- Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge (See Figure F).
- Keep needle pointing up and press dose button until 0 mg lines up with pointer (See Figure G). Repeat steps C and D, up to 6 times, until a drop of Victoza® appears at the needle tip.

If you still see no drop of Victoza®, use a new pen and contact Novo Nordisk at 1-877-484-2869 or visit victoza.com.

Continue to Step G under “Routine Use” →

Routine Use
Step E. Check the Pen
- Take your Victoza® pen from where it is stored.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your Victoza® pen.
- Pull off pen cap (See Figure H).
- Check Victoza® in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.

Step F. Attach the Needle
- Remove protective tab from outer needle cap.
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure (See Figure I).
- Pull off outer needle cap. Do not throw away (See Figure J).
- Pull off inner needle cap and throw away (See Figure K). A small drop of liquid may appear. This is normal.

Step G. Dial the Dose
- Victoza® pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of Victoza® that is prescribed for you.
- Turn the dose selector until your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L).
- You will hear a “click” every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.
- If you select a wrong dose, change it by turning the dose selector backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Victoza® to come out.

Step H. Injecting the Dose
- Insert needle into your skin in the stomach (abdomen), thigh or upper arm. Use the injection technique shown to you by your healthcare provider. Do not inject Victoza® into a vein or muscle.
- Press down on the center of the dose button to inject until 0 mg lines up with the pointer (See Figure M).
- Be careful not to touch the dose display with your other fingers. This may block the injection.
- Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin (See Figure N).
- Change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.

Step I. Withdraw Needle
- You may see a drop of Victoza® at the needle tip. This is normal and it does not affect the dose you just received. If blood appears after you take the needle out of your skin, apply light pressure, but do not rub the area (See Figure O).

Step J. Remove and Dispose of the Needle
- Carefully put the outer needle cap over the needle (See Figure P).
- Safely remove the needle from your Victoza® pen after each use.

Caring for your Victoza® pen
- After removing the needle, put the pen cap on your Victoza® pen and store your Victoza® pen without the needle attached (See Figure Q).
- Do not try to refill your Victoza® pen – it is prefilled and is disposable.
- Do not try to repair your pen or pull it apart.
- Keep your Victoza® pen away from dust, dirt and liquids.
- If cleaning is needed, wipe the outside of the pen with a clean, damp cloth.
How should I store Victoza®?

**Before use:**
- Store your new, unused Victoza® pen in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC).
- If Victoza® is stored outside of refrigeration (by mistake) prior to first use, it should be used or thrown away within 30 days.
- Do not freeze Victoza® or use Victoza® if it has been frozen. Do not store Victoza® near the refrigerator cooling element.

**Pen in use:**
- Store your Victoza® pen for 30 days at 59ºF to 86ºF (15ºC to 30ºC), or in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC).
- When carrying the pen away from home, store the pen at a temperature between 59ºF to 86ºF (15ºC to 30ºC).
- If Victoza® has been exposed to temperatures above 86ºF (30ºC), it should be thrown away.
- Protect your Victoza® pen from heat and sunlight.
- Keep the pen cap on when your Victoza® pen is not in use.
- Always remove the needle after each injection and store your pen without the needle attached.
  This reduces the risk of contamination, infection, leakage and inaccurate dosing.
- Use a Victoza® pen for only 30 days. Throw away a used Victoza® pen after 30 days, even if some medicine is left in the pen.